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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,070	03/03/2006	Sutisak Kitareewan	DC0266US.NP	5026

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EXAMINER	
MARTIN, PAUL C	
ART UNIT	PAPER NUMBER
1653	

NOTIFICATION DATE	DELIVERY MODE
09/26/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTOactions@licataandtyrrell.com

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/564,070	**Applicant(s)** KITAREEWAN ET AL.
	Examiner PAUL MARTIN	**Art Unit** 1653

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 09 September 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *8*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Rebecca E. Prouty/
Primary Examiner, Art Unit 1652

DETAILED ACTION

Claim 8 is pending in this application and was examined on its merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 8 remains rejected under 35 U.S.C. § 103(a) as being unpatentable over Bard et al. (1977) in view of Yoshida et al. (1996) as evidenced by Adamson (1996) for reasons of record set forth in the prior action.

Response to Arguments

Applicant's arguments filed 09/09/2011 have been fully considered but they are not persuasive.

The Applicant argues that Bard et al. teaches the administration of retinoids at doses of from 2 to 20 μM, which are allegedly not doses that are “clinically useful” as they produce toxicity and undesired clinical result (Remarks, Pg. 5, Lines 18-31 and Pg. 6, Lines 1-21).

This is not found to be persuasive for the following reasons, as discussed in the prior action, both Bard et al. and Yoshida et al. teach the use of ATRA in "effective amounts" as broadly defined in the instant Specification at Pg. 15, Lines 13-23 as: " In the context of the method of treatment of the present invention, an effective amount of an agent which destabilizes lysosomes is an amount sufficient to effect beneficial or desired results, including clinical results, and, as such, an effective amount of the agent is one which provides an alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable". As evidenced by Adamson, both references teach the use of concentrations of ATRA that meet this broad definition.

In response to applicant's argument that lysosomal destabilization is an attribute allegedly not sought when developing or screening drugs for anti-cancer properties, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See Exparte Obiaya, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant argues that Bard et al. teaches that retinoic acid itself possesses a toxicity profile that involves lysosomal destabilization and that such lysosomal destabilization is not an attribute that would be sought by one of ordinary skill in the art when developing retinoic acid analogs as anti-cancer drugs or in screening drugs for ability to inhibit cancer cell growth as instantly claimed (Remarks, Pg. 6, Lines 22-28).

In response to applicant's argument that the references fail to show certain features of applicant’s invention, it is noted that the features upon which applicant relies (i.e., screening drugs for ability to inhibit cancer cell growth) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The instant method is drawn to only two method steps: determining if an agent destabilizes lysosomes of a cell and increases PML-RARα protein degradation. As discussed in the prior action, the combined method of Bard et al. and Yoshida et al. would serve to identify an agent (retinoic acid) causing the destabilization of lysosomes in cells expressing PML-RARα and inherently increasing lysomal-dependent PML-RARα protein degradation (in addition to many other proteins).

The Applicant argues that Bard et al. teaches away from the instant method which relies on the ability of an agent to destabilize lysosomes within a cell as a desired drug effect and fails to teach or suggest all the limitations of the instant claims, teaches away from the instant method and would not provide a motivation to combine the teaching with other art to arrive at the instant method of identifying agents that could be used clinically to treat cancer (Remarks, Pg. 7, Lines 1-10).

This is not found to be persuasive for the following reasons, as discussed above, it is noted that the features upon which applicant relies (i.e., screening agents that could be used clinically to treat cancer) are not recited in the rejected claim(s). The instant method is drawn to only two method steps: determining if an agent destabilizes lysosomes of a cell and increases PML-RARα protein degradation. As discussed in the prior action and above, the combined method of Bard et al. and Yoshida et al. would serve to identify an agent (retinoic acid) causing the destabilization of lysosomes in cells expressing PML-RARα and inherently increasing lysomal-dependent PML-RARα protein degradation (in addition to many other proteins). There is no teaching away as the Bard et al. reference performs the same method steps as instantly claimed.

The Applicant argues that the combination of Bard et al. and Yoshida et al. fail to teach the limitations of the claim and cites portions of Yoshida et al. as teaching that ATRA accelerates the degradation of PML-RARα in the proteasome pathway. This opposed to the instant method which is directed to identifying agents that induce the lysosome-dependent pathway and therefore "teaches away" from determining whether an agent destabilizes lysosomes and increases lysosomal dependent PML-RARα protein degradation (Remarks, Pg. 7, Lines 11-34 and Pg. 8, Lines 1-31 and Pg. 9, Lines 1-5).

This is not found to be persuasive for the following reasons, as discussed in the prior action, the combination of references does teach the newly claimed limitations. Further, those of ordinary skill in the art would have also been aware that as lysosomes destabilize, they release lysosomal enzymes into the cytosol which would actively degrade any proteins they encounter, including the protein PML-RARα, if present. Therefore, the combined method of Bard et al. and Yoshida et al. would serve to identify an agent (retinoic acid) causing the destabilization of lysosomes in cells expressing PML-RARα and inherently increasing lysomal-dependent PML-RARα protein degradation (in addition to many other proteins). The limitation that the protein degradation be "lysosomal dependent" is inherently met as the destabilization of the lysosomes releases enzymes and would not otherwise occur, making the resulting protein degradation necessarily "lysosomal dependent".
The Applicant argues that Adamson et al. teaches that peak plasma concentrations of ATRA vary widely and nowhere in the reference is indicated that any specific range of plasma concentrations is clinically effective; that patients relapse after treatment, plasma concentrations diminish rapidly and the reference does not teach that the concentrations of the Bard reference would be the plasma level to be clinically useful; that clinically useful levels of ATRA in patients are based on AUC levels in patients, or measure of the total systemic exposure over time not a single plasma level; and that the reference is not defining a specific clinically useful range of drug levels in blood but instead is addressing the problems encountered with ATRA related to clinical drug resistance, which allegedly makes identifying clinically useful drug levels in blood almost impossible based on treatment regimens used in 1996 (Remarks, Pg. 9, Lines 6-32 and Pg. 10, Lines 1-38 and Pg. 11, Lines 1-2).

This is not found to be persuasive for the following reasons, as discussed in the prior action, both Bard et al. and Yoshida et al. teach the use of ATRA in "effective amounts" as broadly defined in the instant Specification at Pg. 15, Lines 13-23 as: "In the context of the method of treatment of the present invention, an effective amount of an agent which destabilizes lysosomes is an amount sufficient to effect beneficial or desired results, including clinical results, and, as such, an effective amount of the agent is one which provides an alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable". As evidenced by Adamson, both references teach the use of concentrations of ATRA that meet this broad definition. That is, the reference teaches treatment with ATRA at a range of 0.1 to 8 μM (covering both Bard and Yoshida) is a potent remission agent, at least temporarily and thus meets the limitations of being "clinically useful".

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL MARTIN whose telephone number is (571)272-3348. The examiner can normally be reached on M-F 12pm-8pm.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sue Liu can be reached on 571-272-5539. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Paul C Martin/
Examiner, Art Unit 1653
09/16/2011